DETAILED ACTION

1. Applicant's amendment and response filed 3/29/11 is acknowledged and has been entered.

2. The Declaration under 35 USC 1.132 of Inventor Katsuyoshi Matsunami filed on 3/29/11 is acknowledged and has been entered.

3. Applicant is reminded Applicant's election with traverse of Group I and species of an HLA-E chimeric molecule replacing all or part of the α2 domain with all or part of the α2 domain of an HLA-G1 molecule in Applicant's amendment and response filed 7/15/10.

Applicant is reminded that upon consideration of the art, examination had been extended to include the species recited in claim 1 at part (2), *i.e.,* a HLA-E chimeric molecule with the signal peptide of HLA-G1 and a portion of the alpha 2 domain of HLA-E replaced with a part of the alpha 2 domain of HLA-G1.

Claim 1, in part as it pertains to part "(1)" "(a)", and claim 6 read upon the elected species. Claim 1 (in part as it reads upon part "(1)" "(b)", "(2)" and "(3)") and claims 4, 5 and 7-9 are also being included in examination.

Accordingly, claims 2 and 3 (non-elected groups II and III) and claim 10 (non-elected species of Group I) are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 1 and 4-9 are presently being examined.

4. Applicant's amendment has overcome the prior rejection of record of claim 1 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

5. Applicant's amendment filed 3/29/11 has overcome the prior rejection of record of claim 1 under 35 U.S.C. 102(b) as being anticipated by Strong *et al* (J. Biol. Chem. 2/14/03, 278(7): 5082-5090) as evidenced by an admission in the specification at SEQ ID NO: 13 of the sequence listing and as evidenced by Matsunami *et al* (J. Biochem. 2008, 143: 641-647). The art does not meet the presently recited claim limitations, *i.e.,* the art teaches a single amino acid residue change at one position (107) of the α2 domain that is replaced with the corresponding amino acid residue of HLA-G1, whereas the presently amended claims require either all of the a2 domain be replaced with the corresponding HLA-G1 α 2 domain, or a part of the α 2 domain that is replaced includes position 147, or that if all or part of the α2 domain is replaced, the SP of HLA-E that corresponds to SEQ ID NO: 1 also be replaced.

6. The Declaration under 35 USC 1.132 of Inventor Katsuyoshi Matsunami filed on 3/29/11 is sufficient to overcome the prior rejection of record of claim 1 under 35 U.S.C. 102(a) as being anticipated by Matsunami *et al* (Transplantation, 78(2), page 157, Abstract O401, July 27, 2004, of record).

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following are new grounds of rejection necessitated by Applicant's amendment filed 3/29/11.

8. Claims 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an HLA-E chimeric molecule that has all of the α2 domain, the latter part of the α2 domain, or the first portion of the latter part of the α2 domain, replaced with the corresponding domain portion of HLA-G1, and including optionally replacement of the SP of HLA-E with the HLA-G1 signal sequence (SP) that is SEQ ID NO: 21 (and/or optionally replacement of serine 11 in the α1 domain of HLA-E) with that of alanine 11 of HLA-G1, does not reasonably provide enablement for an HLA-E chimeric molecule that has the signal peptide replaced with SEQ ID NO: 21/and/or the aforementioned residue 11 replaced and a portion of the α2 domain that is not one of the aforementioned portions.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification has not enabled the breadth of the claimed invention because the claims encompass an HLA-E chimeric molecule that cannot be expressed or adequately expressed on a cell surface (see below).

The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed compositions can be made and/or used.

The disclosed use for the HLA-E chimeric molecule is to express it on the surface of a xenogenic cell in order to suppress NK cytotoxicity against said xenogenic cell for the purpose of xenotransplantation (especially page 2 at the first full paragraph through page 4 at the second full paragraph). The specification further discloses working examples of chimeric HLA-E molecules in which the SP of HLA-G1 replaces the SP of HLA-E, and additionally, the entire α2 region is replaced with that of HLA-G1, or the latter part of the α2 region is replaced with that of HLA-G1 or the fore part of this latter part of the α2 region is replaced with that of HLA-G1 (see Table 1 on page 11).

When the inventors replaced the latter part of α2 domain with the corresponding part of HLA-G1 (also replaced the SP of HLA-G1 with the SP of HLA-E), or when they replaced the α1 domain with the corresponding part of HLA-G1, cell surface expression was not increased over that seen with native HLA-E (see Table 11).
Evidentiary reference Matsunami *et al* (BBRC, 2006, 347: 692-697, of record) teach that when the α1 domain of HLA-E is replaced with that of HLA-G1, there is no cell surface expression of the chimeric HLA-E molecule (especially Figure 1 and page 694 at the first paragraph of the Results section). Matsunami *et al* also teach the importance of the first portion of the latter half of the α2 domain, particularly residue 147 in cell surface expression (see especially second paragraph of results section and Figure 1).

Thus, it is unpredictable if an HLA-E chimeric molecule that has the first portion of the α2 domain, or the first portion of the α2 domain and a part of the α1 domain, replaced with the corresponding domain portion of HLA-G1 can be used for the disclosed purpose of cell surface expression and inhibition of NK cell activity in xenotransplantation.

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1 and 4-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

a. Claim 1 is indefinite in the recitation of "serine 147" and "cysteine 147" because it is not clear what is meant, *i.e.,* what "147" is in relationship to HLA-E or HLA-G1, respectively, in the absence of a recitation of a SEQ ID NO.

b. Claim 9 is indefinite in the recitation of "serine 147" and "cysteine 147" because it is not clear what is meant, , *i.e.,* what "147" is in relationship to HLA-E or HLA-G1, respectively, in the absence of a recitation of a SEQ ID NO.

c. Claim 7 is indefinite in the recitation of "the latter part of the α2 domain" because it is not clear what is meant, *i.e.,* it is not clear what the latter part of the α2 domain of either HLA-E or HLA-G1 are. Although the instant specification (at page 8, section (2)) discloses that the latter part of the alpha 2 domain of HLA-E is amino acid residues 137-182, there is no reference to a SEQ ID NO corresponding to HLA-E, and there is no disclosure of what the latter part of the alpha 2 domain of HLA-G1 is.

d. Claim 8 is indefinite in the recitation of "the first portion of the latter part of the α2 domain" because it is not clear what is meant, *i.e.,* it is not clear what the first portion of the latter part of the alpha 2 domain is with relation to HLA-E or HLA-G1. Although the instant specification discloses (on page 8, section (3)) that the forepart of the latter part of the alpha 2 domain is amino acid residues 137-150, there is no reference to a SEQ ID NO, and there is no disclosure of what the first portion of the latter part of the alpha 2 domain of HLA-G1 is.

e. Claims 4 and 5 are indefinite in the recitation of "amino acid number 147 of the α2 domain" because it is not clear what is meant, *i.e.,* what "147" is in relationship to HLA-E or HLA-G1, respectively, in the absence of a recitation of a SEQ ID NO.

11. No claim is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Phuong "Neon" Huynh, can be reached on 571-272-0846. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you

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